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Regional Localization of an X-Linked Mental Retardation Gene to Xp21.1–Xp22.13 (MRX38)

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A gene responsible for X-linked mental retardation with macrocephaly and seizures (MRX38) in a family with five affected males in three generations was localized to Xp21.1–p22.13 by linkage analysis. Recombination events placed the gene between DXS1226 distally and DXS1238 proximally, defining an interval of approximately 14 cM. A peak lod score of 2.71 was found with several loci in Xp21.1 (DXS992, DXS1236, DXS997, and DXS1036) at a recombination fraction of zero. The map intervals of 5 X-linked mental retardation loci, MRX2 (Xp22.1–p22.2), MRX19 (Xp22), MRX21 (Xp21.1–p22.3), MRX29 (Xp21.2–p22.1), and MRX32 (Xp21.2–p22.1), and two syndromal mental retardation loci, Partington syndrome (PRTS; Xp22) and Coffin-Lowry syndrome (CLS; Xp22.13–p22.2), overlap this region. As none of these display the same phenotype seen in the family reported here, this X-linked mental retardation locus may represent a new entity.

KEY WORDS: XLMR, MRX38, X-linked mental retardation, Xp21.1–Xp22.13, seizures, macrocephaly

INTRODUCTION

The incidence of X-linked mental retardation has been estimated at approximately 1/600 male births. Of these, 25–40% represent cases of fragile X syndrome [Sutherland and Hecht, 1985]. The remainder of X-linked mental retardation cases may be subdivided into other recognized syndromal forms, if consistent phenotypic characteristics are present, or non-specific forms, if mental retardation is the only consistent trait among affected individuals (Table I). The most recent comprehensive list of X-linked mental retardation includes 127 syndromal and non-specific entities [Neri et al., 1994]. Owing to the difficulties in clinical definition of mental retardation entities with inconsistent phenotypic characteristics, the grouping of families for the purpose of linkage analysis is unwise. For this reason, only mapping information from sufficiently informative single families (lod score +2.0 or greater) [Mulley et al., 1992] is used. The disease locus segregating in such a family is assigned a sequential MRX designation. Thus, a single mental retardation gene may acquire several different designations in independent families.

Of the MRX loci given a regional assignment by linkage analysis, most map to the pericentric region. We report here an X-linked mental retardation locus (MRX38) mapping to Xp21.1–p22.13, and examine the overlap in clinical characteristics and genetic locations between this and other mental retardation conditions mapped to this region.

MATERIALS AND METHODS

Clinical Data

The pedigree of the family examined is presented in Figure 1. The pedigree shows the segregation of an X-linked recessive disorder, with transmission through unaffected carrier females to six affected males in three generations. All affected males show mild to moderate mental handicap with particular abnormalities with speech. No specific facial or other physical anomalies were seen, with the exception of macrocephaly in all affected males, who, in addition, experienced seizures at some stage in life, to varying degrees.

Photographs of the affected individuals in this family are shown in Figure 1. Individual II-10 (Fig. 2a), age 49 years, was always severely delayed, had some speech

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TABLE I. Phenotypic Characteristics Observed in Affected Individuals

	Individual II-3	Individual II-10	Individual III-3	Individual III-6	Individual III-13	Individual IV-2
Age (years)	Deceased	49	36	34	24	14
Seizures	+	+	+	+	+	+
OFC (cm)	Not available	59.5	58.4	58.4	60.9	55.5 at 7 years
(centile)		>98	>98	>98	>98	>98
Height (cm)	Not available	Not available "normal"	166	166	173	118 at 7 years
centile			<3	<3	10	3

and poor hand use. Seizures began at age 6 years but with treatment are now rare. He has not walked for several years and has lost all speech. He has marked pes cavus with high arches and clawed toes, and a large head circumference (59.5 cm; >98th centile), but no other phenotypic abnormalities.

Individual III-3 (Fig. 2b), age 36 years, has had seizures from an early age, is mildly delayed, walks, talks with stuttering, and is able to perform some manual work. He has had no schooling. He has a large head circumference (58.4 cm; >98th centile).

III-6 (Fig. 2c), age 34 years, has education to Grade 7 and can read and write a little, had seizures only in childhood, and has a head circumference of 58.4 cm (>98th centile).

III-13 (Fig. 2d), age 24 years, has global developmental delay with particular speech problems. At 9 years he had several grand mal seizures and remains on anticonvulsants although he has been seizure-free for years. He attended school and reads and writes to some extent, has poor speech and stutters. He is cheerful, outgoing and athletic. His head circumference measures 60.9 cm (>98th centile).

IV-2, age 14 years, has global delay. He was first seen at age 3 months when developmental delay and macrocephaly (95th centile) were noted. He had poor head control, generalized mild hypertonia, brisk reflexes, and an abnormal EEG with a paroxysmal event suggesting seizure, though none was seen clinically. A CT scan at that time was normal. Although he showed some evidence of early seizures, he is now seizure-free and is doing well in special education in Grade 7.

DNA Analysis

Genomic DNA was obtained from peripheral lymphocytes by standard phenol-chloroform extraction. The polymerase chain reaction was used to amplify microsatellite alleles from 50 ng genomic DNA, using specified conditions in a Perkin Elmer/Cetus 400 or 480 thermal cycler, with 28 cycles of denaturation (94C°, 1′), annealing (52–60C°, 1′), and extension (72C°, 1′), followed by a final extension (72C°, 10′). Alleles at the FMR-1 and FRAXE loci were amplified using published conditions [references in Table II]. α^{32}P-dCTP was incorporated into the PCR products. Reaction products were separated on 6% polyacrylamide, 8 M urea sequencing gels and detected by autoradiography. Alleles were numbered in order of decreasing size, or sized by comparison to a control sequence, for each locus.

Two-point linkage analyses were performed using MLINK of the LINKAGE software package, assuming X-linked recessive inheritance.

RESULTS

The family was initially screened with a series of highly polymorphic microsatellite markers distributed along the entire length of the X chromosome. No evidence of linkage was observed at any of 12 markers in Xq, but linkage was suggested in Xp, leading us to use further microsatellite markers to refine the localization and identify key recombination events (Table II). Pairwise lod scores are given in Table III for the mental retardation locus against 23 markers in Xp and 12 markers in Xq, ordered Xpter-Xcen-Xqter. The relative order of these markers was determined by physical and genetic mapping [Willard et al., 1994; Wang et al., 1994]. The highest lod score, $z_{max} = 2.71$ was obtained with the dinucleotide repeat markers DXS992, DXS1236, DXS997, and DXS1036, each at $\theta = 0.00$. This is equal to the highest z_{max} expected for this family using the samples available, as all obligate carriers were informative at these loci. Haplotype analysis was used to determine the most likely phases in the females, and to identify crossover events between marker loci (Figure 3). A recombination event in individual III-13 places the disease locus proximal to DXS1226 in Xp22.13, while another recombination event in individual IV-2 places the locus distal to DXS1238 in Xp21.1. Together these two boundaries define genetic and physical intervals of approximately 14 cM and 9 Mb, respectively.

DISCUSSION

X-linked mental retardation is a heterogeneous disorder. Once cases of fragile X syndrome are removed, a large number of mental retardation entities exist which appear to be distinct on the basis of either genetic localization or phenotype. The difficulties in defining clear, consistent phenotypes prevents the grouping of families demonstrating clinical similarities. However, the limited genetic information available even from fairly large single pedigrees, makes precise mapping of X-linked mental retardation loci difficult, resulting in

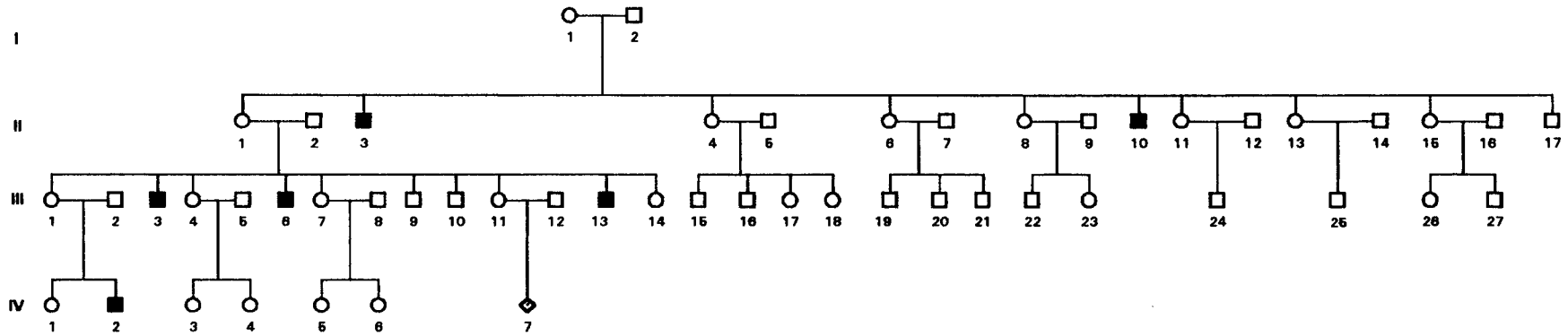


Fig. 1. Pedigree structure of the MRX38 family.

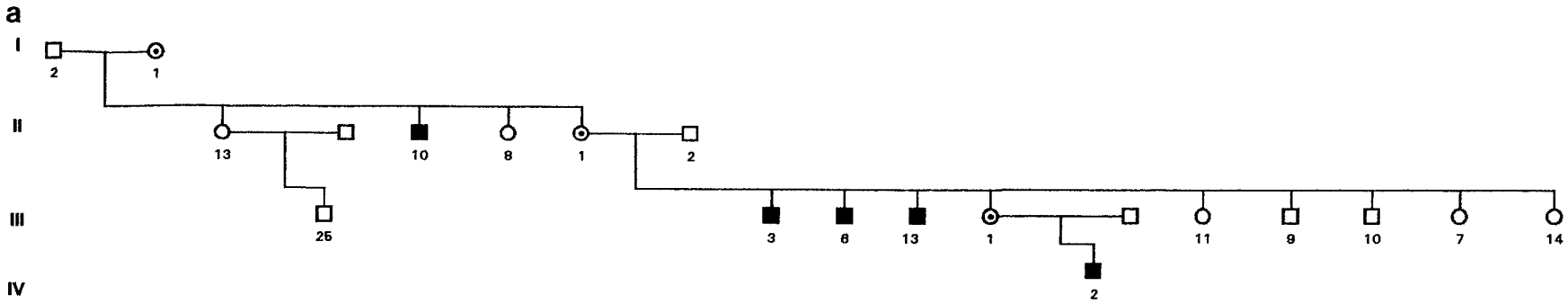
Fig. 2. Five of the six affected males in family MRX38. **a**: Individual II-10. **b**: Individual III-3. **c**: Individual III-6. **d**: Individual III-13. **e**: Individual IV-2.

relatively large map intervals for MRX entities. In many instances, these intervals overlap for different MRX loci; more precise localization with new markers or ultimately cloning of MRX genes will be necessary in order to determine which MRX entities arise from mutations in the same genes.

The peak lod score obtained for the family described here exceeds +2.0. Thus this locus obtained the designation MRX38. Recombination events in affected individuals define the candidate region between DXS1226 distally and DXS1238 proximally, in Xp21.1-p22.13. This region includes the 3′ end of the gene responsible for Duchenne and Becker muscular dystrophies, and overlaps the map intervals for two syndromal MR entities, Partington syndrome (PRTS) [Partington et al., 1988] and Coffin-Lowry syndrome (CLS) [Temtamy et al., 1975], as well as five non-specific mental retardation loci, MRX2 [Hu et al., 1994], MRX19 [Donelly et al., 1994], MRX21 [Kozak et al., 1993], MRX29 [Häne

Fig. 3. Genetic analysis of MRX38 family. **a**: The individuals available for genotypic examination. **b**: Haplotype analysis in this family, from distal (top) to proximal (bottom). The haplotype associated with MRX38 derived from individual I:1 is indicated by the dark box. The region shared by all affected males and not present in unaffected males, and therefore the candidate region for the disease locus, is delimited by DXS1238 proximally and DXS1226 distally.

a



b

	I:2	I:1		II:13		III:25	II:10	II:8		II:1		II:2	III:3	III:6	III:13	III:1		IV:2	III:11		III:9	III:10	III:7		III:14	
KAL 5'	4	1	2	4	2	2	2	4	2	4	1	3	1	4	1	3	1	3	3	1	4	4	3	4	3	1
DXS 1224	2	1	2	2	2	2	1	2	2	2	1	2	1	2	1	2	1	2	2	2		2	2	2	2	1
DXS 987	3	1	3	3	3	3	1	3	3	3	1	2	1	3	1	2	1	2	2	3	3	3	2	3	2	1
DXS 207	3	2	1	3	1	1	2	3	1	3	2	4	2	3					4	3	3	3	4	3	4	2
DXS 1053	3	2	3	3	3	3	2	3	3	3	2	1	2	3	2	1	2	1	1	3	3	3	1	3	1	2
DXS 418	2	1	1	2	1	1	1	2	1	2	1	3	1	2	1	3	1	3	3	2	2	2	3	2	3	1
DXS 999	2	1	1	2	1	1	1	2	1	2	1	1	1	2	1	1	1	1	1	2	2	2	1	2	1	1
DXS 443	1	2	2	1	2	2	2	1	2	1	2	3	2	1	2	3	2	2	3	1	1	1	3	1	3	2
DXS 1229	1	1	2	1	2	2	1	1	2	1	1	2	1	1	1	2	1	1	2	1	1	1	2	1	2	1
DXS 1226	3	2	1	3	1	1	2	3	1	3	2	1	2	3	2	1	2	2	1	3	3	3	1	3	1	2
DXS 989	1	1	3	1	3	3	1	1	3	1	1	2	1	1	1	2	1	1	2	1	1	1	2	1	2	1
DXS 1061	3	3	2	3	2	2	3	3	2	3	3	1	3	3	3	1	3	3	1	3	3	3	1	3	1	3
DXS 1202	2	1		2	1	1	1	2	1	2	1	1	1	1	1	1	1	1	1	2	2	2	1	2	1	1
DXS 992	3	2	4	3	4	3	2	3	4	3	2	1	2	2	2	1	2	2	1	3	3	3	1	3	1	2
DXS 1236	2	1	3	2	3	2	1	2	3	2	1	4	1	1	1	4	1	1	4	2	2	2	4	2	4	
DXS 997	3	2	3	3	3	3	2	3	3	3	2	1	2	2	2	1	2	2	1	3	3	3	1	3	1	2
DXS 1237	1	2	1	1	1	1	2	1	1	1	2	2	2	2	2	2	2	2	2	1	1	1	2	1	2	2
DXS 1036	2	1	2	2	2	2	1	2	1	2	1	2	1	1	1	2	1	1	2	2	2	2	2	2	2	1
DXS 1238	3	2	1	3	1	3	2	3	1	3	2	4	2	2	2	4	2	4	4	3	3	3	4	3	4	2
5' DMD	2	3	1	2	1	2	3	2	1	2	3	3	3	3	3	3	3	3	3	2	2	2	3	2	3	3
DXS 538	2	1	3	2	3	2	1	2	3	2	1	4	1	1	1	4	1	4	4	2	2	2	4	2	4	1
DXS 7	2	1	1	2	1	2		2	1	2	1	3	2	1	1	3	1	3	3	2	2	2	3		3	2
DXS 988	1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	2	1	2	2	1	1	1	2	1	2	1

Fig. 3.

TABLE II. X-Linked PCR-Based Polymorphic Loci Used in Linkage Analysis*

KAL 5′	Xp22.32	Bouloux et al., Nucl. Acids Res. 19, 5453 [1991]
DXS 1224	Xp22.31	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 987	Xp22.2	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 207	Xp22.2	Oudet et al., J. Med. Genet. 30, 300–303 [1992]
DXS 1053	Xp22.2	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 418	Xp22.13	Van de Vosse et al., Hum. Mol. Genet. 2, 2202 [1993]
DXS 999	Xp22.13	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 443	Xp22.13	Browne et al., Hum. Mol. Genet. 1, 213 [1992]
DXS 1229	Xp22.13	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 1226	Xp22.13	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 989	Xp22.12	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 1061	Xp22.11	Gyapay et al., Nat. Genet. 7, 246–338 (1994)
DXS 1202	Xp22.11	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 992	Xp21.2	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 1236	Xp21.1	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 997	Xp21.1	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 1237	Xp21.1	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 1036	Xp21.1	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
DXS 1238	Xp21.1	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
5′ DMD	Xp21.1	Hugnot et al., Nucl. Acids Res. 19, 3159 [1991]
DXS 538	Xp21.1	Browne et al., Nucl. Acids Res. 19, 1161 [1991]
DXS 7	Xp11.4	Moore et al., Nucl. Acids Res. 20, 929 [1992]
DXS 988	Xp11.22	Gyapay et al., Nat. Genet. 7, 246–338 [1994]
ARA	Xq12	Edwards et al., Genomics 12, 241–253 [1992]
DXS 453	Xq13.1	Weber et al., Nucl. Acids Res. 18, 4037 [1990]
DXS 441	Xq13.2	Ram et al., Nucl. Acids Res. 20, 1428 [1992]
DXS 3	Xq21.33	Stainer et al., Nucl. Acids Res. 19, 4793 [1991]
DXS 458	Xq21.33	Weber et al., Nucl. Acids Res. 18, 4037 [1990]
DXS 454	Xq22.1	Weber et al., Nucl. Acids Res. 18, 4037 [1990]
DXS 294	Xq26.3	Gedeon et al., Nucl. Acids Res. 19, 5087 [1991]
DXS 102	Xq26.3	Gedeon et al., Am. J. Med. Genet. 43, 255–260 [1992]
FMR-1	Xq27.3	Fu et al., Cell 67,6, 1047–1058 [1991]
FRAXE	Xq28	Sutherland and Baker, Hum. Mol. Genet. 1, 111–113 [1992]
DXS 1113	Xq28	Weber et al., Hum. Mol. Genet. 2, 5, 612 [1993]
GABRA3	Xq28	Hicks et al., Nucl. Acids Res. 19, 4016 [1991]

*Loci are ordered Xpter-Xcen-Xqter.

et al., 1996a], and MRX32 [Howard-Peebles et al., 1979; Häne et al., 1996b]. PRTS, described as a syndrome of mental retardation, dystonic movements of the hands and dysarthria, has been mapped between DXS365 and DXS28, with a peak lod score at DXS989 [Gedeon et al., 1994]. The manifestations of CLS include a characteristic facial appearance and minor manifestations in females suggesting X-linked dominant inheritance. The CLS locus was mapped between Afm291*wf*5 and DXS1683 in Xp22.13 [Biancalana et al., 1994]. The mental retardation disorder described here does not show X-linked dominant inheritance or the physical characteristics of either CLS or PRTS, and therefore is unlikely to reflect a new family with either of these conditions.

The linkage interval for MRX19 is defined by KAL and DXS989, so that the overlap with MRX38 spans the approximately 3cM region between DXS1226 and DXS989. Since MRX19 results in mild mental retardation in carrier females [Choo et al., 1984], it does not appear to be the same entity as MRX38. The family in which MRX2 was mapped to the DXS365–DXS989 interval [Hu et al., 1994] contained two affected males with large heads and seizures, but also included females described as slow and macroorchidism in affected males [Proops et al., 1983], findings which are not present in the family described here. The overlap between these two candidate regions is limited by DXS1226 and DXS989. Kozak et al. [1993] described a family with four male mentally retarded patients with a characteristic face, two mildly retarded obligate carrier females with no phenotypic abnormalities. This locus, subsequently designated MRX21, was mapped to Xp21.1–p22.3, and on the basis of the characteristic face and affected females would appear to represent a distinct entity from MRX38. The MRX29 locus was mapped to Xp21.2–p22.1 and is described to cause severe mental retardation [Hane et al., 1995], unlike the moderate phenotype observed in this family. MRX32 leads to mental retardation of variable severity, apparently without any other abnormalities, and has been localized to Xp21.2–p22.1 as well [Howard-Peebles et al., 1979; Häne et al., 1996b]. Phenotypically, MRX29 and MRX32 appear distinct from MRX38.

The disorder described here, consisting of mental retardation and macrocephaly as the only consistent finding, and designated MRX38, thus appears to represent a new non-specific X-linked mental retardation entity, clinically distinct from other previously described mental retardation syndromes in the Xp21.1–p22.13 region.

TABLE III. Two-Point Lod Scores for MRX38 With Markers in Xp

θ	0	0.05	0.1	0.15	0.2	0.3	0.4
KAL 5′	−∞	−1.61	−0.82	−0.42	0.67	0.07	0.11
DXS 1224	−∞	−0.33	0.14	0.34	0.43	0.43	0.28
DXS 987	−∞	−0.05	0.39	0.57	0.63	0.58	0.36
DXS 207	−∞	0.67	0.83	0.86	0.83	0.65	0.38
DXS 1053	−∞	−0.05	0.39	0.57	0.63	0.58	0.36
DXS 418	−∞	−0.61	−0.12	0.11	0.22	0.29	0.2
DXS 999	−∞	0.11	0.32	0.4	0.42	0.36	0.22
DXS 443	−∞	0.67	0.83	0.86	0.83	0.65	0.38
DXS 1229	0.6	0.56	0.51	0.46	0.41	0.29	0.16
DXS 1226	−∞	1.23	1.34	1.32	1.24	0.95	0.54
DXS 989	0.6	0.56	0.51	0.46	0.41	0.29	0.16
DXS 1061	0.6	0.56	0.51	0.46	0.41	0.29	0.16
DXS 1202	1.81	1.67	1.53	1.38	1.22	0.88	0.48
DXS 992	2.71	2.51	2.3	2.07	1.84	1.32	0.71
DXS 1236	2.71	2.51	2.3	2.07	1.84	1.32	0.71
DXS 997	2.71	2.51	2.3	2.07	1.84	1.32	0.71
DXS 1237	2.41	2.23	2.04	1.84	1.63	1.17	0.63
DXS 1036	2.71	2.51	2.3	2.07	1.84	1.32	0.71
DXS 1238	−∞	1.23	1.34	1.32	1.24	0.95	0.54
5′ DMD	−∞	1.23	1.34	1.32	1.24	0.95	0.54
DXS 538	−∞	1.23	1.34	1.32	1.24	0.95	0.54
DXS 7	−∞	−0.61	−0.12	0.11	0.22	0.29	0.2
DXS 988	0.3	0.28	0.26	0.23	0.2	0.15	0.08

The actual number of loci in this region responsible for X-linked disorders with mental retardation as a component is unknown, and awaits the more precise localization and cloning of X-linked mental retardation genes.

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